REMARKS

Status of the Claims

Claims 1-43 are currently pending. Claims 5-8, 15, 17-27, and 30-42 were withdrawn from further consideration in response to a restriction requirement by the Examiner, under 37 C.F.R. §1.142(b).

In the present Response, claims 5-8, 15, 17-27, and 30-42 are cancelled, without prejudice; claims 1, 3, 4, 10, 11, 14, 16, 28, 29, and 43 are amended; and new claims 44-50 are added. Thus, after entry of these amendments, claims 1-4, 9-14, 16, 28-29, and 43- 50 are presented for consideration.

Pursuant to the Office Action, claims 1-3, 9-14, 16, 28-29, and 43 are rejected under 35 U.S.C. §101. Claims 1-3, 9-14, 16, 28-29, and 43 are rejected under 35 U.S.C. §112; first paragraph. Applicants respectfully traverse all objections to the specification and rejection of the claims.

Support for the Claim Amendments

Support for the amendment to claim 1 can be found *inter alia,* on page 4, lines 19-23; page 5, lines 1-2 and lines 15-21; and page 23, lines 20-23. Support for the amendment to claim 3 can be found, *inter alia,* on page 2, line 14. Claim 4 is amended to be in independent form. Support for new claims drawn to nucleic acids encoding for SEQ ID NO:4 and nucleic acids having at least 75% identity to the same can be found, *inter alia,* on pages 2, lines 7-8, and claim 1 as originally filed. Support for new claims drawn to the method of diagnosing or determining a predisposition for GCA can be found, *inter alia,* on page 5, lines 5-21, and in originally filed claims 34 and 35. No new matter has been introduced by the present amendments.

Rejoining of process claims under *In re Ochiai*

In response to a Restriction Requirement, Applicants elected Group II, drawn to the embodiment of SEQ ID NO:3, including claims 1-4, 9-16, 28, and 29. Thus, among others, claims 34 and 35 were withdrawn from consideration and cancelled in the present claim. Applicants seek to reintroduce amended versions of claim 34 and 35 in new claims 46 and 47.

Applicants respectfully request that, as claim 4, as amended, has been found allowable and after the elected product claims have been found to be allowable, the withdrawn process (methods) claims which depend from or otherwise include all of the limitations of the allowed product claims be rejoined. MPEP §821.04 (7th Ed., Revision 1, Feb. 2000); *In re Ochiai*, 37 USPQ2d 1127 (Fed. Cir. 1995); *In re Brouwer*, 37 USPQ2d 1663 (Fed. Cir. 1995); 1184 OG 86, 3/26/96.

Informalities

Applicants thank the Examiner for acknowledging that the application appears to be in sequence compliance, Applicants' IDS has been received, and formal drawings have been approved by the Draftsperson.

Applicants have amended the specification to provide a more descriptive title. Applicants have also amended the specification to provide a more descriptive abstract. Applicants submit that the new title and abstract should overcome the present objections to the specification.

Applicants have also amended the specification to correct minor errors, of which they are aware.

Applicants have deleted the reference to the hyperlink on page 22, line 26.

Applicants have rewritten claim 4 in independent form, removing the objection to claim 4, which has otherwise been found allowable.

Applicants submit that the above amendments remove all outstanding objections raised in the Office Action. Accordingly, Applicants request reconsideration and removal of these objections to the application.

Rejection under 35 U.S.C. §101

Claims 1-3, 9-14, 16, 28-29, and 43 are rejected under 35 U.S.C. §101 for allegedly being unsupported by either a specific and substantial, credible asserted utility or a well established utility. Applicants respectfully traverse this rejection.

Applicants thank the Patent Office for recognizing that SEQ ID NO:3 has specific and substantial, credible utility. However, the Patent Office alleges that "[b]ecause the specification does not appear to teach the structural basis for the differential antibody recognition of the polypeptide encoded by residues 1-369 of SEQ ID NO:3 (i.e., SEQ ID NO:4), it does not appear that the utility established for SEQ ID NO:3 can be extended to isolated nucleic acid or recombinant nucleic acids having 75, 85, or even 95% identity to SEQ ID NO:3; nucleic acids which hybridize to SEQ ID NO:3 (other than those comprising SEQ ID NO:3 itself); fragments of various lengths of hybridizing nucleic acids or nucleic acids having 75% identity to SEQ ID NO:3; expression vectors or transformed cells comprising nucleic acid variants of SEQ ID NO:3, or for methods for producing a polypeptide comprising a variant of SEQ ID NO:4."[1] Based on this assertion, the Patent Office concludes that claims 1-3, 9-14, 16, 28-29, and 43 lack utility.

A claim will be rejected under 35 U.S.C. §101 for lack of utility only if no credible, specific, and substantial utility is asserted in the specification or no well established utility is found. MPEP 2107.

Applicants aver, however, that these claims possess the utility required under section 101. One of the utilities of Applicants' claimed invention is that the nucleic acids can be used to diagnose and/or detect Giant Cell Arthritis (GCA) or a predisposition for developing GCA in an individual.

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[1] See page 3, lines 25-32, of the Office Action.

In analyzing the requirements of the 35 U.S.C. §101 utility requirement, Applicants look to the Synopsis of Application of the Revised Interim Utility Guidelines found on the U.S. Patent and Trademark Office website.

Specific utility. The utility of the claim must be specific to the subject matter claimed. Here, the claims are drawn to nucleic acids that can be used to diagnose or determine a predisposition for developing GCA. The presence of the GCA-associated nucleic acids or proteins is indicative of GCA or a predisposition for developing GCA. As the specification provides a specific utility for the claimed subject matter, e.g., nucleic acids for diagnosing GCA, the requirement of specific utility is met.

Substantial utility. The utility of the claim must define a "real world" use. Here, the claims are drawn to nucleic acids that can be used to diagnose GCA. GCA is a particular disease condition. Identifying those who suffer from it, or those who are predisposed to suffer from it, can greatly aid in treating and/or preventing this condition. Accordingly, the disclosed use of the claimed invention is substantial and "real world."

Credible utility. Once an applicant has asserted a particular utility, that assertion is credible unless (A) the logic underlying the assertion is seriously flawed, or (B) the facts upon which the assertion is based are inconsistent with the logic underlying the assertion. A credible utility is assessed from the standpoint of whether a person of ordinary skill in the art would accept that the recited or disclosed invention is currently available for such use.

The credibility of the presently stated utility is supported by a Rule 132 declaration filed by Dr. Gordon, submitted herewith, references to be supplied under separate cover. She, as one skilled in the art, declares that the use of nucleic acids and PCR techniques in the detection and diagnosis of disease is well known. Furthermore, she has provided evidence showing how such use can be employed to diagnose GCA.

Moreover, Dr. Gordon declares that the claimed invention has well-established utility. A well-established utility is "a specific, substantial, and credible utility which is well known, immediately apparent, or implied by the specification's disclosure of the properties of a material,

alone or taken with the knowledge of one skilled in the art." This utility of using nucleic acids to diagnose GCA is not the " 'throw away' utility that one can dream up for an invention or a nonspecific utility that would apply to virtually every member of a general class of materials, such as proteins or DNA" that is referred to in the guidelines. For example, Dr. Gordon has provided experimental evidence, see Exhibit A of the Declaration, that detects an approximately 405 bp nucleotide in subjects determined to have GCA that cannot be detected in subjects determined not to have GCA.

Accordingly, amended claims 1-4, 9, 10, 16, 28-29, and new claims 44-50 possess the required utility in that the claimed nucleic acids can be used in the diagnosis of GCA. The kits of claim 28 and 29 are just one embodiment of the invention that can be used to practice the claimed invention. Amended claims 11-14 also possess the requisite utility in that they can be used to propagate DNA, via the transformed cell, and generate probes for GCA diagnosis, via nick translation or *in vitro* transcription while in a plasmid such as an expression vector. Amended claim 43, amended to depend from newly submitted claim 45, also possesses utility as its claims is directed to nucleic acids that encode for the polypeptide having the amino acid sequence of SEQ ID NO:4. Applicants have shown the utility of the polypeptide comprising the sequence of SEQ ID NO:4 in the diagnosis of GCA, see for example, Example 2 of the specification.

In light of the reasons and amendments provided above, Applicants submit that, claims 1-4, 9-14, 16, 28-29 and 43-45 all possess utility as defined in 35 U.S.C. §101. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection based upon 35 U.S.C. §101 for allegedly lacking utility as applied to claims 1-4, 9-14, 16, 28-29, and 43.

Rejection under 35 U.S.C. §112, first paragraph

Claims 1-3, 9-14, 16, 28-29 and 43 are also rejected under 35 U.S.C. §112, first paragraph, because it is alleged that since the claimed invention is not supported by either a specific and substantial, credible asserted utility or a well established utility, one skilled in the art clearly would not know how to use the claimed invention.

Applicants respectfully submit, in the preceding section, they have shown the requisite utility of claims 1-3, 9-12, 14, 16, 28-29 and 43 to overcome the rejection based on 35 U.S.C. §101.

The Patent Office further alleges that the skilled artisan would consider it to be unpredictable as to which primer pair would detect for the presence of a nucleic acid sequence *in situ*, and, thus, experimentation left to those skilled in the art, would still be unnecessarily, and improperly, extensive and undue.

The Federal Circuit in *In re Wands* directed that the focus of the enablement inquiry should be whether the experimentation needed to practice the invention is or is not "undue" experimentation. The court set forth specific factors to be considered.

One of these factors is "the quantity of experimentation necessary." Guidance as to how much experimentation may be needed and still not be "undue" is set forth by the Federal Circuit in, e.g., *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*[2] An applicant there had claims that were generic to all IgM antibodies directed to a specific antigen. However, only a single antibody producing cell line had been deposited.[3] The PTO had rejected claims that were generic to all antibodies directed to the antigen as lacking an enabling disclosure.

The Federal Circuit reversed, noting that the evidence indicated that those skilled in the monoclonal antibody art could, using the state of the art and applicants' written disclosure, produce and screen new hybridomas secreting other monoclonal antibodies falling within the genus without undue experimentation. The court held that applicants' claims need not be limited to the specific, single antibody secreted by the deposited hybridoma cell line (significantly, the genus of antibodies was allowed even though only one antibody specie was disclosed). The court was acknowledging that, because practitioners in that art are prepared to screen large numbers of negatives in order to find a sample that has the desired properties, the screening that would be necessary to make additional antibody species was not "undue experimentation."

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2 Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), cert. denied, 480 U.S. 947 (1987).

3 The cell line was a hybridoma, thus, all of the antibodies it produced had the same structure and activity.

Analogously, practitioners in the present field recognize the need for a certain amount of testing or screening to arrive at optimal conditions for hybridization and the like. However, the procedures for these determinations are widely accepted, routine protocols, not requiring "undue experimentation" to be practiced.

Applicants have amended claim 1 to require that the nucleic acid be capable of hybridizing to a nucleic acid associated with GCA. It is known that specific binding can be accomplished with at least 60.7% homology to the target nucleic acid sequence, see Rule 132 Declaration by Dr. Gordon. Because of this, it is appropriate to claim at least 75% identity to SEQ ID NO:3 to cover the scope of the claimed invention.

It should be noted that the level of skill for one in this particular art is high. With practical knowledge gained from working in the field and extensive guidance of hybridization technology from references such as Tijssen, Techniques in Biochemistry and Molecular Biology Hybridization with Nuclease Probes, "Overview of Principles in Hybridization and the Strategy of Nucleic Acid Assays" (1993), and Applicants' application, at least at pages 20-24 and pages 68-70, it would be readily apparent to one of ordinary skill in the art, the conditions under which nucleic acids and PCR primers will hybridize to the analyte of interest. Accordingly, one skilled in the art has sufficient guidance by the specification to practice the claimed methods without undue experimentation.

Claims 1-3, 9-14, 16, 28-29 and 43 are rejected under 35 U.S.C. §112 first paragraph, for allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The Patent Office alleges that there does not appear to be an adequate written description in the specification as filed of the essential structural features of a polypeptide encoded by recited nucleic acid. It is further alleged that although the specification discloses the nucleic acid sequence of SEQ ID NO:3, no function is provided for this open reading frame, other than that when expressed as GST-fusion protein it is found preferentially by antibodies from the sera

of GCA patients and the structural property of SEQ ID NO:3 that provide this activity does not appear to be disclosed.[4]

Applicants respectfully aver that there is more than adequate written description in the specification to practice the claimed invention. The claims recite nucleic acids with at least 75, 85, 95% identity to SEQ ID NO:3, or nucleic acids which encode for a polypeptide comprising a sequence as set forth in SEQ ID NO:4 or having 75% identity to the latter referred to nucleic acids. The claimed nucleic acids can be used as probes to indicate the presence of the disease GCA or a predisposition to developing GCA. As for claim 43, the amino acid sequence of SEQ ID NO:4 provides an adequate description of the claimed polypeptide.

The claimed invention is directed to compositions and methods for detecting nucleic acids, including the exemplary nucleic acid SEQ ID NO:3, detectable in the disease GCA. Applicants have shown that levels of SEQ ID NO:3 are increased in GCA. Accordingly, a further description of the biological function of the protein encoded by SEQ ID NO:3 is not necessary for the specification to meet the requirements of section 112, first paragraph.

Consequentially, Applicants respectfully aver that, after reconsideration of the outstanding issues in light of these arguments, the disclosure and the instant amendment, the rejection of claims under section 112, first paragraph, can be properly withdrawn.

CONCLUSION

Claims 1-43 are pending in the application. Claims 5-8, 15, 17-27, and 30-42 have been cancelled, without prejudice; claims 1, 3, 4, 10, 11, 14, 16, 28, 29, and 43 have been amended; and claims 44-50 have been added by the present Response. Applicants request that the Examiner reconsider the application and claims in light of the foregoing reasons and amendments and respectfully submit that the claims are in condition for allowance.

If, in the Examiner's opinion, a telephonic interview would expedite the favorable prosecution of the present application, the undersigned attorney would welcome the opportunity

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[4] See page 5, second full paragraph from top of the Office Action.

to discuss any outstanding issues and to work with the Examiner toward placing the application in condition for allowance.

Attached is a marked-up version of the changes being made by the current amendment.

Applicants believe that no fees are necessitated by the present Response. However, in the event any fees are due, the Commissioner is hereby authorized to charge any such fees to Deposit Account No. 06-1050.

Respectfully submitted,

Date: 20 March 2002

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Version with markings to show changes made

In the specification:

The Title of the invention found on the application cover sheet and page 1, lines 1-2 has been amended as follows:

[NOVEL GENES AND POLYPEPTIDES] NUCLEIC ACIDS FOR THE DIAGNOSIS AND TREATMENT OF GIANT CELL ARTERITIS

Paragraph beginning at page 1, line 11 has been amended as follows:

Giant cell arteritis (GCA) is a systemic vasculitis that is a serious and potentially blinding rheumatologic disease of the elderly. Current treatment of GCA requires systemic immunosuppression with profound morbidity in the affected elderly population. GCA is widely believed to be immune-mediated; however, the etiology and pathogenesis of this systemic vasculitis remains unidentified. Furthermore, diagnosis of GCA is difficult because it relies on a constellation of nonspecific signs and symptoms and a diagnostic arterial biopsy. Significantly, blindness may be the first symptom of GCA. Thus, if a way [was] were found to better diagnose or even screen for early onset or predisposition for GCA at an earlier stage of the disease, many cases of blindness and many lives would be saved.

Paragraph beginning at page 1, line 20 has been amended as follows:

Currently, corticosteroids are critical in the treatment of giant cell arteritis; they reduce the incidence of blindness and rapidly relieve symptoms. However, the amounts of steroids (e.g., prednisone) needed are significant and not without side effects[;], particularly as they usually must be given over an extended period of time, usually about two years. Steroid treatment is not uniformly effective and causes significant morbidity in up to 40% of patients because of hypertension, osteoporosis, infection, glucose dysregulation, fluid overload, and aseptic necrosis of the hip or shoulder. Alternative use of nonsteroidal anti-inflammatory drugs (NSAIDs) will lessen the painful symptoms, but they do not prevent the blindness or vascular problems.

Accordingly, new methods of treating GCA are needed. The present invention addresses these and other needs.

Paragraph beginning on page 4, line 25 has been amended as follows:

The invention also provides kits, e.g., ELISA kits, for detecting the presence of human antibodies associated with GCA in a sample comprising a polypeptide of the invention. The polypeptides or peptides in the kit can be immobilized. The kit can further comprise a non-human antibody or [an] antisera that specifically binds to a human antibody under [an] *in situ* or *in vitro* conditions. As described below, the non-human antibody in the kit can further comprise a detectable tag (e.g., an enzyme, a radionuclide, biotin, and the like, as discussed below), or the invention can comprise a second antibody capable of binding to the first non-human antibody.

Paragraph beginning on page 5, line 5 has been amended as follows:

The invention provides methods for diagnosing or determining predisposition for GCA comprising the following steps: (a) providing an antibody that specifically binds to a polypeptide associated with GCA, wherein the antibody has the same specificity as an antibody of the invention (that binds to a GCA-associated peptide or polypeptide); or, a nucleic acid that can detectably hybridizes to a nucleic acid of the invention under *in situ* or *in vitro* conditions; (b) providing a tissue or fluid (e.g., whole blood, serum or urine) sample; (c) contacting the antibody or nucleic acid with the sample; and (d) detecting whether the antibody specifically binds to a polypeptide in the tissue or serum sample or the nucleic acid hybridizes to a nucleic acid in the tissue or serum sample; wherein the specific binding or hybridization is diagnostic for or determines a predisposition for GCA.[.]

Paragraph beginning on page 5, line 30 has been amended as follows:

The invention provides methods for isolating nucleic acid sequences associated with GCA comprising the following steps: (a) providing a first tissue sample from a tissue or fluid specimen not showing histologic or other signs of GCA and a second tissue sample from a tissue or fluid specimen showing histologic or other signs of GCA; (b) isolating the nucleic acid from both samples; (c) sub[s]tracting nucleic acid from the first sample from the second sample to

isolate nucleic acid only present in the second sample, wherein the isolated nucleic acid from the second sample is associated with GCA-affected tissue and not normal tissue. This aspect of the invention can incorporate all variations and equivalents of sub[s]tractive hybridization techniques, as described below. In this method, the first and the second tissue sections can be taken from a "skip" lesion of a temporal artery of a GCA patient.

Paragraph beginning on page 8, line 10 has been amended as follows:

The invention is based on the discovery that novel sequences can be associated with GCA lesions. While the invention is not limited by any particular theory or mechanism, these unique-GCA associated sequences may be associated with a pathology initiating or causative microorganism. Accordingly, subtractive hybridization of normal (non-involved) from GCA-involved tissue led to the discovery of the novel GCA-associated sequences of the invention. Translation of exemplary sequences to recombinant polypeptides (in the form of fusion proteins for convenience of isolation and manipulation) led to the discovery that GCA patients have circulating antibodies that specifically bind to the polypeptides of the invention. Accordingly, the peptides and polypeptides of the invention are used in kits and methods for diagnosing GCA by identifying circulating anti-GCA antibodies in the serum, urine or tissue samples of patients. Because blindness may be the first presenting symptom of GCA, the diagnostic methods of the invention can be used to screen for GCA on patients that, while having no symptoms of GCA, do have a relatively high probability of suffering from GCA, such as elderly patients.

Paragraph beginning on page 19, line 15 has been amended as follows:

One exemplary means to biopsy, or isolate, GCA lesions is by dissection with laser-capture microdissection (LCM)[.], [E]either freshly biopsied or archival pathology specimens of GCA-positive arteries from both histopathologically involved and uninvolved areas. Because the vasculitis of GCA occurs in an irregular, or discontinuous pattern (the [c]so-called "skip lesion"), isolation of one artery (or vein, if appropriate) sample can yield both involved and uninvolved tissue samples. Retrieval of selected cells is achieved by activation of a transfer film placed in contact with a tissue section, by a laser beam (30 or 60 micron diameter) that is focused on a selected area of tissue using an inverted microscope. In LCM, a thermoplastic polymer coating

(e.g., ethylene vinyl acetate) attached to a rigid support is placed in contact with a tissue section. The EVA polymer over microscopically selected cell clusters is precisely activated by a near-infrared laser pulse and bonds to the targeted area. Removal of the EVA and its support from the tissue section procures the selected cell aggregates for molecular analysis. A computer-controlled arm can precisely position a 40-micron-wide strip of a cylindrical EVA surface onto a sample with a light contact force. Techniques of laser-capture microdissection are known in the art, e.g., the PixCell laser capture microdissection (LCM) system, see, e.g., Kohda (2000) Kidney Int. 57:321-331; Goldsworthy (1999) Mol. Carcinog. 25:86-91; Banks (1999) Electrophoresis 20:689-700; Emmert-Buck (1996) Science 274:998-1001; U.S. Patent Nos. 5,985,085; 5,859,699.

Paragraph beginning on page 20, line 5 has been amended as follows:

Nucleic acids within the scope of the invention include isolated or recombinant nucleic acids which specifically hybridize[s] to an exemplary nucleic acid of the invention. Stringent conditions are sequence-dependent and will be different in different circumstances. Longer sequences hybridize specifically at higher temperatures. An extensive guide to the hybridization of nucleic acids is found in Tijssen, Techniques in Biochemistry and Molecular Biology--Hybridization with Nucleic Probes, "Overview of principles of hybridization and the strategy of nucleic acid assays" (1993). Generally, stringent conditions are selected to be about 5 to 10°C lower than the thermal melting point (Tm) for the specific sequence at a defined ionic strength and pH. The Tm is the temperature (under defined ionic strength, pH, and nucleic acid concentration) at which 50% of the probes complementary to the target hybridize to the target sequence at equilibrium (as the target sequences are present in excess, at Tm, 50% of the probes are occupied at equilibrium). Stringent conditions will be those in which the salt concentration is less than about 1.0 M sodium ion, typically about 0.01 to 1.0 M sodium ion concentration (or other salts) at pH 7.0 to 8.3 and the temperature is at least about 30°C for short probes (*e.g.*, 10 to 50 nucleotides) and at least about 60°C for long probes (*e.g.*, greater than 50 nucleotides). Stringent conditions may also be achieved with the addition of destabilizing agents such as formamide.

Paragraph beginning on page 27, line 3 has been amended as follows:

Another example of an algorithm that is suitable for determining percent sequence identity (*i.e.*, substantial similarity or identity) in this invention is the BLAST algorithm, which is described in Altschul (1990) *J. Mol. Biol.* 215:403-410. Software for performing BLAST analyses is publicly available through the National Center for Biotechnology Information [(http://www.ncbi.nlm.nih.gov/)]. This algorithm involves first identifying high scoring sequence pairs (HSPs) by identifying short words of length W in the query sequence, which either match or satisfy some positive-valued threshold score T when aligned with a word of the same length in a database sequence. T is referred to as the neighborhood word score threshold (Altschul (1990) *supra*). These initial neighborhood word hits act as seeds for initiating searches to find longer HSPs containing them. The word hits are then extended in both directions along each sequence for as far as the cumulative alignment score can be increased. Cumulative scores are calculated using, for nucleotide sequences, the parameters M (reward score for a pair of matching residues; always > 0) and N (penalty score for mismatching residues, always < 0). For amino acid sequences, a scoring matrix is used to calculate the cumulative score. Extension of the word hits in each direction are halted when: the cumulative alignment score falls off by the quantity X from its maximum achieved value; the cumulative score goes to zero or below, due to the accumulation of one or more negative-scoring residue alignments; or the end of either sequence is reached. The BLAST algorithm parameters W, T, and X determine the sensitivity and speed of the alignment. In one embodiment, to determine if a nucleic acid sequence is within the scope of the invention, the BLASTN program (for nucleotide sequences) is used incorporating as defaults a wordlength (W) of 11, an expectation (E) of 10, M=5, N=4, and a comparison of both strands. For amino acid sequences, the BLASTP program uses as default parameters a wordlength (W) of 3, an expectation (E) of 10, and the BLOSUM62 scoring matrix (see, *e.g.*, Henikoff (1989) Proc. Natl. Acad. Sci. USA 89:10915).

Paragraph beginning on page 66, line 7 has been amended as follows:

In various embodiments of the invention, the polypeptides (or peptides) and antibodies of the invention are immobilized to the "capture" GCA-associated antibodies or polypeptides, respectively. Additional reagents are added to this reaction to detect any specific binding. These

so-called "sandwich assays" are commercially useful for detecting or isolating protein or antibodies.

Paragraph beginning on page 67, line 14 has been amended as follows:

Immunoassays can be either competitive or noncompetitive. Noncompetitive immunoassays are assays in which the amount of captured analyte (GCA-associated human antibody) is directly measured. In one "sandwich" assay, for example, the capture agent (a polypeptide or peptide of the invention) can be bound directly to a solid substrate where they are immobilized. These immobilized reagents then capture antibody present in the test sample. The antibody thus immobilized is then bound by a labeling agent, such as a second anti-human antibody reagent bearing a label. Alternatively, the human antibody binding reagent can lack a label, but it may, in turn, be bound by a labeled third reagent (e.g. another antibody), e.g., specific to antibodies of the species from which the second antibody is derived. The second (or third) can be modified with a detectable moiety, such as biotin, to which [a] another labeled molecule can specifically bind, such as, e.g., enzyme-labeled streptavidin. In a variation of the above, the immobilized reagent can be an antibody of the invention used to capture a GCA-associated polypeptide. The second (soluble) reagent can be, e.g., another GCA-associated polypeptide binding antibody of the invention. Competitive binding assays can also be used. For example, a known amount of labeled human antibody is added to the serum or tissue sample. The sample is then contacted with the capture agent (GCA-associated polypeptides or peptides of the invention). The amount of labeled human antibody bound to the immobilized reagent is inversely proportional to the concentration of GCA-polypeptide reactive antibody present in the sample. A hapten inhibition assay is another competitive assay.

Paragraph beginning on page 74, line 18 has been amended as follows:

Pharmaceutically acceptable carriers can contain a physiologically acceptable compound that acts, e.g., to stabilize the composition or to increase or decrease the absorption of the agent and/or pharmaceutical composition. Physiologically acceptable compounds can include, for example, carbohydrates, such as glucose, sucrose, or dextrans, antioxidants, such as ascorbic acid or glutathione, chelating agents, low molecular weight proteins, compositions that reduce the

clearance or hydrolysis of any co-administered agents, or excipients or other stabilizers and/or buffers. Detergents can also be used to stabilize the composition or to increase or decrease the absorption of the pharmaceutical composition (see infra for exemplary detergents).

Paragraph beginning on page 76, line 24 has been amended as follows:

The pharmaceutical compositions of the invention (e.g., therapeutic antibodies, vectors or antisense oligonucleotides) can be delivered by any means known in the art systemically (e.g., intravenously), regionally, or locally (e.g., intra- or peri-tumoral or intracystic injection, e.g., to treat bladder cancer) by, e.g., intraarterial, intratumoral, intravenous (IV), parenteral, intra-pleural cavity, topical, oral, or local administration, as subcutaneous, intra-tracheal (e.g., by aerosol) or transmucosal (e.g., buccal, bladder, vaginal, uterine, rectal, nasal mucosa), intra-tumoral (e.g., transdermal application or local injection). For example, intra-arterial injections can be used to have a "regional effect," e.g., to focus on a specific organ (e.g., brain, liver, spleen, lungs)[.], [F]for example, intra-hepatic artery injection or intra-carotid artery injection. If it is desired to deliver the preparation to the brain, it can be injected into a carotid artery or an artery of the carotid system of arteries (e.g., occipital artery, auricular artery, temporal artery, cerebral artery, maxillary artery, etc.).

Paragraph beginning on page 79, line 15 has been amended as follows:

Thirty sequentially cut tissue sections (10 μm each) were placed on non-charged microscope slides, fixed, dehydrated, and stained with hematoxylin and eosin. GCA inflammatory lesions were identified and dissected using a Laser Capture Microdissecting Microscope™ (Arcturus Engineering, Inc., Mountain View, CA). Approximately 500 cells including giant cells and inflammatory infiltrate were dissected from each GCA specimen. DNA isolated from these cells represented the "tester" population. Approximately 500 cells were microdissected from a subsequent section with no histopathologic evidence of GCA lesions. The DNA isolated from these cells represented the "driver" sample in the RDA.

Paragraph beginning on page 80, line 12 has been amended as follows:

One criterion [to] for selecting which genes would first be translated into recombinant polypeptides and used to analyze for the presence of human antibodies in serum from GCA patients was relative homology to sequences of known microbial origin. A total of eleven unique DNA sequences were obtained in the first two RDAs using two different GCA+ arterial specimens. Sequence identity analysis showed that four of the unique sequences, GCA 1, GCA 5, GCA 14, and GCA 17, may be distantly related to known microbial sequences. Thus, these were the first sequences selected for further characterization.

Paragraph beginning on page 83, line 4 has been amended as follows:

Human sera was tested in triplicate at multiple dilutions in 0.05% Tween20 –PBS. Reactivity was detected with an alkaline-phosphatase-labeled goat anti-human IgG and developed with Sigma 104 phosphatase substrate. Absorbances [was] were measured at 405 nm with a Biorad ELISA reader and Macintosh analytic software. OD values of nonspecific binding of sera to GST alone [was] were subtracted from the raw values of binding to the GST-GCA fusion proteins in order to determine specific absorbances.

In the claims:

Claims 5-8, 15, 17-27, and 20-42 have been cancelled.

Claims 1, 3, 4, 10, 11, 14, 16, 28, 29, and 43 have been amended as follows:

-- 1. (Twice Amended) An isolated or recombinant nucleic acid comprising: a nucleic acid sequence having at least 75% sequence identity to SEQ ID NO:3 wherein the nucleic acid is capable of identifying or detecting a GCA associated nucleic acid.[or a nucleic acid encoding a polypeptide, wherein the polypeptide has a sequence as set forth in SEQ ID NO:4.]

3. (Twice Amended) The nucleic acid of claim 2, wherein the sequence identity to SEQ ID NO:3 is at least 95%.

4. (Twice Amended) An isolated or recombinant nucleic acid comprising [The nucleic acid of claim 3, wherein the nucleic acid comprises] a sequence as set forth in SEQ ID NO:3.

10. (Twice Amended) The nucleic acid of claim 1, claim 4, [or] claim 9, claim 44 or claim 45, wherein the nucleic acid is between about 15 and about 200 residues in length; is between about 25 and about 100 residues in length; or is between about 35 and about 75 residues in length.

11. (Twice Amended) An expression vector comprising at least one nucleic acid operably linked to a promoter, wherein the nucleic acid comprises a sequence as set forth in claim 1, claim 4, [or] claim 9, claim 44 or claim 45.

14. (Twice Amended) A transformed cell comprising the nucleic acid of claim 1, claim 4, [or] claim 9, claim 44 or claim 45.

16. (Twice Amended) A polymerase chain reaction (PCR) primer pair that can amplify a nucleic acid sequence as set forth in claim 1, claim 4, [or] claim 9, claim 44 or claim 45, or a subsequence thereof, under *in situ* or *in vitro* conditions.

28. (Twice Amended) A kit for detecting the presence of nucleic acid sequences associated with GCA in a sample comprising a nucleic acid as set forth in claim 1, claim 4, [or] claim 9, claim 44 or claim 45, wherein the nucleic acid of the sample detectably hybridizes to a nucleic acid as set forth in claim 1, claim 4, [or] claim 9, claim 44 or claim 45 under *in situ* or *in vitro* conditions.

29. (Twice Amended) A kit for detecting the presence of nucleic acid sequences associated with GCA in a sample comprising an amplification primer pair that can amplify a nucleic acid in the sample having a sequence as set forth in claim 1, claim 4, [or] claim 9, claim 44 or claim 45 under *in situ* or *in vitro* conditions.

43. (Amended) A method of producing a polypeptide having an amino acid sequence comprising SEQ ID NO:4, comprising:

expressing the nucleotide of claim 45 [1 or claim 9].

In the abstract:

The abstract has been amended as follows:

This invention provides [novel genes and polypeptides] nucleic acids and methods for making and using them. The compositions and methods of the invention are used to diagnose and treat Giant Cell Arteritis (GCA).